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WARNINGS

Patients treated with parenteral aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use. Safety for treatment periods which are longer than 14 days has not been established.

Neurotoxicity, manifested as vestibular and permanent bilateral auditory ototoxicity, can occur in patients with preexisting renal damage and in patients with normal renal function treated at higher doses and/or for periods longer than those recommended. The risk of aminoglycoside-induced ototoxicity is greater in patients with renal damage. High frequency deafness usually occurs first and can be detected only by audiometric testing. Vertigo may occur and may be evidence of vestibular injury. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching and convulsions. The risk of hearing loss due to aminoglycosides increases with the degree of exposure to either high peak or high trough serum concentrations. Patients developing cochlear damage may not have symptoms during therapy to warn them of developing eighth-nerve toxicity, and total or partial irreversible bilateral deafness may occur after the drug has been discontinued. Aminoglycoside-induced ototoxicity is usually irreversible.

Aminoglycosides are potentially nephrotoxic. The risk of nephrotoxicity is greater in patients with impaired renal function and in those who receive high doses or prolonged therapy.

Neuromuscular blockade and respiratory paralysis have been reported following parenteral injection, topical instillation (as in orthopedic and abdominal irrigation or in local treatment of empyema), and following oral use of aminoglycosides. The possibility of these phenomena should be considered if aminoglycosides are administered by any route, especially in patients receiving anesthetics; neuromuscular blocking agents such as tubocurarine, succinylcholine, decamethonium; or in patients receiving massive transfusions of citrate-anticoagulated blood. If blockage occurs, calcium salts may reverse these phenomena, but mechanical respiratory assistance may be necessary.

Renal and eighth-nerve function should be closely monitored especially in patients with known or suspected renal impairment at the onset of therapy and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Serum concentrations of amikacin should be monitored when feasible to assure adequate levels and to avoid potentially toxic levels and prolonged peak concentrations above 35 micrograms per mL. Urine should be examined for decreased specific gravity, increased excretion of proteins and the presence of cells or casts. Blood urea nitrogen, serum creatinine or creatinine clearance should be measured periodically. Serial audiograms should be obtained where feasible in patients old enough to be tested, particularly high risk patients. Evidence of ototoxicity (dizziness, vertigo, tinnitus, roaring in the ears and hearing loss) or nephrotoxicity requires discontinuation of the drug or dosage adjustment.

Concurrent and/or sequential systemic, oral or topical use of other neurotoxic or nephrotoxic products, particularly bacitracin, cisplatin, amphotericin B, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin or other aminoglycosides should be avoided. Other factors that may increase risk of toxicity are advanced age and dehydration. The concurrent use of amikacin with potent diuretics (ethacrynic acid or furosemide) should be avoided since diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

DESCRIPTION

Amikacin sulfate is a semi-synthetic aminoglycoside antibiotic derived from kanamycin.

$\text{D-Streptamine, } 0\text{-}3\text{-amino-}3\text{-deoxy-}\alpha\text{-D-glucopyranosyl-(1\#6)0-[6-amino-6-deoxy-}\alpha\text{-D-glucopyranosyl-(1\#4)]-N}^1\text{-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy-, (S)-, sulfate (1:2) (salt).}$

Gram-negative

Amikacin is active *in vitro* against *Pseudomonas* species, *Escherichia coli*, *Proteus* species (indole-positive and indole-negative), *Providencia* species, *Klebsiella-Enterobacter-Serratia* species, *Acinetobacter* (formerly *Mima-Herellea*) species and *Citrobacter freundii*.

When strains of the above organisms are found to be resistant to other aminoglycosides, including gentamicin, tobramycin and kanamycin, many are susceptible to amikacin *in vitro*.

Gram-positive

Amikacin sulfate is active *in vitro* against penicillinase and non-penicillinase-producing *Staphylococcus* species, including methicillin-resistant strains. However, aminoglycosides in general have a low order of activity against other Gram-positive organisms, viz., *Streptococcus pyogenes*, enterococci and *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*).

Amikacin resists degradation by most aminoglycoside inactivating enzymes known to affect gentamicin, tobramycin and kanamycin.

In vitro studies have shown that amikacin sulfate combined with a beta-lactam antibiotic acts synergistically against many clinically significant Gram-negative organisms.

Disc Susceptibility Test

Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure¹ has been recommended for use with discs to test susceptibility to amikacin. Interpretation involves correlation of the diameters obtained in the disc test with MIC values for amikacin. When the causative organism is tested by the Kirby-Bauer* method of disc susceptibility, a 30 mcg amikacin disc should give a zone of 17 mm or greater to indicate susceptibility. Zone sizes of 14 mm or less indicate resistance. Zone sizes of 15 to 16 mm indicate intermediate susceptibility. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

1Bauer, A.W., Kirby, W.M.M., Sherris, J.C., and Turck, M.: Antibiotic Testing by a Standardized Single Disc Method, *Am. J. Clin. Pathol.*, 45:493, 1966; Standardized Disc Susceptibility Test, *FEDERAL REGISTER*, 37:2057-29, 1972.

INDICATIONS AND USAGE

Amikacin sulfate injection is indicated in the short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria, including *Pseudomonas* species, *Escherichia coli*, species of indole-positive and indole-negative *Proteus*, *Providencia* species, *Klebsiella-Enterobacter-Serratia* species and *Acinetobacter* (*Mima-Herellea*) species.

Clinical studies have shown amikacin sulfate injection to be effective in bacterial septicemia (including neonatal sepsis); in serious infections of the respiratory tract, bones and joints, central nervous system (including meningitis) and skin and soft tissue; intra-abdominal infections (including peritonitis); and in burns and post-operative infections (including post-vascular surgery). Clinical studies have shown amikacin also to be effective in serious complicated and recurrent urinary tract infections due to these organisms. Aminoglycosides, including amikacin sulfate injection, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity.

Bacteriologic studies should be performed to identify causative organisms and their susceptibilities to amikacin. Amikacin may be considered as initial therapy in suspected Gram-negative infections, and therapy may be instituted before obtaining the results of susceptibility testing. Clinical trials demonstrated that amikacin was effective in infections caused by gentamicin-and/or tobramycin-resistant strains of Gram-negative organisms, particularly *Proteus rettgeri*, *Providencia stuartii*, *Serratia marcescens* and *Pseudomonas aeruginosa*. The decision to continue therapy with the drug should be based on results of the susceptibility tests, the severity of the infection, the response of the patient and the important additional considerations contained in the **WARNINGS box** above.

Amikacin has also been shown to be effective in staphylococcal infections and may be considered as initial therapy under certain conditions in the treatment of known or suspected staphylococcal disease such as, severe infections where the causative organism may be either a Gram-negative bacterium or a staphylococcus, infections due to susceptible strains of staphylococci in patients allergic to other antibiotics, and in mixed staphylococcal/Gram-negative infections.

In certain severe infections such as neonatal sepsis, concomitant therapy with a penicillin-type drug may be indicated because of the possibility of infections due to Gram-positive organisms such as streptococci or pneumococci.

CONTRAINDICATIONS

A history of hypersensitivity to amikacin is a contraindication for its use. A history of hypersensitivity or serious toxic reactions to aminoglycosides may contraindicate the use of any other aminoglycoside because of the known cross-sensitivities of patients to drugs in this class.

WARNINGS

See **WARNINGS box** above.

Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycosides cross the placenta and there have been several reports of total irreversible, bilateral congenital deafness in children whose mothers received streptomycin during pregnancy. Although serious side effects to the fetus or newborns have not been reported in the treatment of pregnant women with other aminoglycosides, the potential for harm exists. Reproduction studies of amikacin have been performed in rats and mice and revealed no evidence of impaired fertility or harm to the fetus due to amikacin. There are no well-controlled studies in pregnant women, but investigational experience does not include any positive evidence of adverse effects to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than nonasthmatic people.

PRECAUTIONS

Aminoglycosides are quickly and almost totally absorbed when they are applied topically, except to the urinary bladder, in association with surgical procedures. Irreversible deafness, renal failure and death due to neuromuscular blockade have been reported following irrigation of both small and large surgical fields with an aminoglycoside preparation. Amikacin sulfate injection is potentially nephrotoxic, ototoxic and neurotoxic. The concurrent or serial use of other ototoxic or nephrotoxic agents should be avoided either systemically or topically because of the potential for additive effects. Increased nephrotoxicity has been reported following concomitant parenteral administration of aminoglycosides, antibiotics and cephalosporins. Concomitant cephalosporins may spuriously elevate creatinine determinations.

Since amikacin is present in high concentrations in the renal excretory system, patients should be well-hydrated to minimize chemical irritation of the renal tubules. Kidney function should be assessed by the usual methods prior to starting therapy and daily during the course of treatment.

If signs of renal irritation appear (casts, white or red cells or albumin), hydration should be increased. A reduction in dosage (see **DOSAGE AND ADMINISTRATION**) may be desirable if other evidence of renal dysfunction occurs such as decreased creatinine clearance; decreased urine specific gravity; increased BUN, creatinine or oliguria. If azotemia increases or if a progressive decrease in urinary output occurs, treatment should be stopped.

Note: When patients are well hydrated and kidney function is normal, the risk of nephrotoxic reactions with amikacin is low if the dosage recommendations (see **DOSAGE AND ADMINISTRATION**) are not exceeded.

Elderly patients may have reduced renal function which may not be evident in routine screening tests such as BUN or serum creatinine. A creatinine clearance determination may be more useful. Monitoring of renal function during treatment with aminoglycosides is particularly important.

Aminoglycosides should be used with caution in patients with muscular disorders such as myasthenia gravis or parkinsonism since these drugs may aggravate muscle weakness because of their potential curare-like effect on the neuromuscular junction.

In vitro mixing of aminoglycosides with beta-lactam antibiotics (penicillin or cephalosporins) may result in a significant mutual inactivation. A reduction in serum half-life or serum level may occur when an aminoglycoside or penicillin-type drug is administered by separate routes. Inactivation of the aminoglycoside is clinically significant only in patients with severely impaired renal function. Inactivation may continue in specimens of body fluids collected for assay, resulting in inaccurate aminoglycoside readings. Such specimens should be properly handled (assayed promptly, frozen or treated with betalactamase).

Cross-allergenicity among aminoglycosides has been demonstrated.

As with other antibiotics, the use of amikacin may result in overgrowth of non-susceptible organisms. If this occurs, appropriate therapy should be instituted.

Aminoglycosides should not be given concurrently with potent diuretics. (See **WARNINGS box**.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in humans have not been performed with the aminoglycosides to determine their effect on carcinogenesis, mutagenesis or impairment of fertility.

Pregnancy

Category D (see **WARNINGS** section).

Nursing Mothers

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Pediatric Use

Aminoglycosides should be used with caution in premature and neonatal infants because of the renal immaturity of these patients and the resulting prolongation of serum half-life of these drugs.

ADVERSE REACTIONS

All aminoglycosides have the potential to induce auditory, vestibular and renal toxicity and neuromuscular blockade. (See **WARNINGS box**.) They occur more frequently in patients with present or past history of renal impairment, of treatment with other ototoxic or nephrotoxic drugs and in patients treated for longer periods and/or with higher doses than recommended.

Neurotoxicity-Ototoxicity

Toxic effects on the eighth cranial nerve can result in hearing loss, loss of balance, or both. Amikacin primarily affects auditory function. Cochlear damage includes high frequency deafness and usually occurs before clinical hearing loss can be detected.

Neurotoxicity-Neuromuscular Blockade

Acute muscular paralysis and apnea can occur following treatment with aminoglycoside drugs.

Nephrotoxicity

Elevation of serum creatinine, albuminuria, presence of red and white cells, casts, azotemia and oliguria have been reported. Renal function changes are usually reversible when the drug is discontinued.

Other

In addition to those described above, other adverse reactions which have been reported on rare occasions are skin rash, drug fever, headache, paresthesia, tremor, nausea and vomiting, eosinophilia, arthralgia, anemia and hypotension.

OVERDOSAGE

In the event of overdosage or toxic reaction, peritoneal dialysis or hemodialysis will aid in the removal of amikacin from the blood. In the newborn infant, exchange transfusion may also be considered.

DOSAGE AND ADMINISTRATION

The patient's pretreatment body weight should be obtained for calculation of correct dosage. Amikacin sulfate injection may be given intramuscularly or intravenously.

The status of renal function should be estimated by measurement of the serum creatinine concentration or calculation of the endogenous creatinine clearance rate. The blood urea nitrogen (BUN) is much less reliable for this purpose. Reassessment of renal function should be made periodically during therapy.

Whenever possible, amikacin concentrations in serum should be measured to assure adequate but not excessive levels. It is desirable to measure both peak and trough serum concentrations intermittently during therapy. Peak concentrations (30–90 minutes after injection) above 35 mcg/mL and trough concentrations (just prior to the next dose) above 10 mcg/mL should be avoided. Dosage should be adjusted as indicated.

Intramuscular Administration for Patients with Normal Renal Function

The recommended dosage for adults, children and older infants (see **WARNINGS box**) with normal renal function is 15 mg/kg/day divided into 2 or 3 equal doses administered at equally divided intervals, i.e., 7.5 mg/kg q12h or 5 mg/kg q8h. Treatment of patients in the heavier weight classes should not exceed 1.5 g/day.

When amikacin is indicated in newborns (see **WARNINGS box**), it is recommended that a loading dose of 10 mg/kg be administered initially to be followed with 7.5 mg/kg every 12 hours.

The usual duration of treatment is 7 to 10 days. It is desirable to limit the duration of treatment to short-term whenever feasible.

The total daily dose by all routes of administration should not exceed 15 mg/kg/day. In difficult and complicated infections where treatment beyond 10 days is considered, the use of amikacin should be reevaluated. If continued, amikacin serum levels and renal, auditory and vestibular functions should be monitored. At the recommended dosage level, uncomplicated infections due to amikacin-sensitive organisms should respond in 24 to 48 hours. If definite clinical response does not occur within 3 to 5 days, therapy should be stopped and the antibiotic susceptibility pattern of the invading organism should be rechecked. Failure of the infection to respond may be due to resistance of the organism or to the presence of septic foci requiring surgical drainage.

When amikacin is indicated in uncomplicated urinary tract infections, a dose of 250 mg twice daily may be used.

DOSAGE GUIDELINES

ADULTS AND CHILDREN WITH NORMAL RENAL FUNCTION

Patient Weight		Dosage	
lbs	kg	7.5 mg/kg q12h	OR 5 mg/kg q8h
99	45	337.5 mg	225 mg
110	50	375 mg	250 mg
121	55	412.5 mg	275 mg
132	60	450 mg	300 mg
143	65	487.5 mg	325 mg

154	70	525 mg	350 mg
165	75	562.5 mg	375 mg
176	80	600 mg	400 mg
187	85	637.5 mg	425 mg
198	90	675 mg	450 mg
209	95	712.5 mg	475 mg
220	100	750 mg	500 mg

Intramuscular Administration for Patients with Impaired Renal Function

Whenever possible, serum amikacin concentrations should be monitored by appropriate assay procedures. Doses may be adjusted in patients with impaired renal function either by administering normal doses at prolonged intervals or by administering reduced doses at a fixed interval.

Both methods are based on the patient's creatinine clearance or serum creatinine values since these have been found to correlate with aminoglycoside half-lives in patients with diminished renal function. These dosage schedules must be used in conjunction with careful clinical and laboratory observations of the patient and should be modified as necessary. Neither method should be used when dialysis is being performed.

Normal Dosage at Prolonged Intervals

If the creatinine clearance rate is not available and the patient's condition is stable, a dosage interval in hours for the normal dose can be calculated by multiplying the patient's serum creatinine by 9. (e.g., if the serum creatinine concentration is 2 mg/100 mL, the recommended single dose (7.5 mg/kg) should be administered every 18 hours.)

Reduced Dosage at Fixed Time Intervals

When renal function is impaired and it is desirable to administer amikacin at a fixed time interval, dosage must be reduced. In these patients, serum amikacin concentrations should be measured to assure accurate administration of amikacin and to avoid concentrations above 35 mcg/mL. If serum assay determinations are not available and the patient's condition is stable, serum creatinine and creatinine clearance values are the most readily available indicators of the degree of renal impairment to use as a guide for dosage.

First, initiate therapy by administering a normal dose, 7.5 mg/kg, as a loading dose. This loading dose is the same as the normally recommended dose which would be calculated for a patient with a normal renal function as described above.

To determine the size of maintenance doses administered every 12 hours, the loading dose should be reduced in proportion to the reduction in the patient's creatinine clearance rate:

$$\frac{\text{Maintenance Dose}}{\text{Every 12 hours}} = \frac{\text{observed CC in mL/min}}{\text{normal CC in mL/min}} \times \text{calculated loading dose in mg}$$

(CC—creatinine clearance rate)

An alternate rough guide for determining reduced dosage at 12-hour intervals (for patients whose steady state serum creatinine values are known) is to divide the normally recommended dose by the patient's serum creatinine.

The above dosage schedules are not intended to be rigid recommendations but are provided as guides to dosage when the measurement of amikacin serum levels is not feasible.

Intravenous Administration

The individual dose, the total daily dose and the total cumulative dose of amikacin sulfate are identical to the dose recommended for intramuscular administration. The solution for intravenous use is prepared by adding the contents of a 500 mg vial to 100–200 mL of sterile diluent such as 0.9% sodium chloride injection or 5% dextrose injection or any other compatible solution.

The solution is administered to adults over a 30 to 60 minute period. The total daily dose should not exceed 15 mg/kg/day and may be divided into either 2 or 3 equally-divided doses at equally-divided intervals.

In pediatric patients, the amount of fluid used will depend on the amount of amikacin sulfate ordered for the patient. It should be a sufficient amount to infuse the amikacin over a 30 to 60 minute period. Infants should receive a 1 to 2 hour infusion.

Amikacin should not be physically premixed with other drugs but should be administered separately according to the recommended dose and route.

Stability in IV Fluids

Amikacin sulfate is stable for 24 hours at room temperature at concentrations of 0.25 and 5 mg/mL in the following solutions:

5% dextrose injection

5% dextrose and 0.2% sodium chloride injection
5% dextrose and 0.45% sodium chloride injection
0.9% sodium chloride injection
lactated Ringer's injection

Normosol® M in 5% dextrose injection
(or Plasma-Lyte 56 injection in 5% dextrose in water).

Normosol® R in 5% dextrose injection
(or Plasma-Lyte 148 injection in 5% dextrose in water).

In the above solutions with amikacin sulfate concentrations of 0.25 and 5.0 mg/mL, solutions aged for 60 days at 4°C and then stored at 25°C had utility times of 24 hours.

At the same concentrations, solutions frozen and aged for 30 days at -15°C, thawed, and stored at 25°C had utility times of 24 hours. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Aminoglycosides administered by any of the above routes should not be physically premixed with other drugs but should be administered separately.

Because of the potential toxicity of aminoglycosides, "fixed dosage" recommendations which are not based upon body weight are not advised. Rather, it is essential to calculate the dosage to fit the needs of each patient.

HOW SUPPLIED

Amikacin Sulfate Injection, USP is supplied as follows:

NDC	Number Strength
0703-9032-03	500 mg per 2 mL
0703-9040-03	1 gram per 4 mL

2 mL and 4 mL vials are packaged in shelf packs of 10.

Store at controlled room temperature 15°–30°C (59°–86°F).

Amikacin Sulfate Injection, USP is supplied as a colorless solution which requires no refrigeration. At times the solution may become a very pale yellow; this does not indicate a decrease in potency.

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Teva Parenteral Medicines, Inc
Irvine, CA 92618

PRINCIPAL DISPLAY PANEL - 500 MG/2 ML VIAL LABEL

NDC 0703-9032-03

Rx only

Amikacin

Sulfate Injection, USP

equivalent to Amikacin

500 mg/2 mL

(250 mg/mL)

2 mL Single Dose Vials

For IM or IV Use

10 Vials

TEVA

NDC 0703-9032-03

Rx only

Amikacin

Sulfate Injection, USP
equivalent to Amikacin

500 mg/2 mL

(250 mg/mL)

2 mL Single Dose Vials
For IM or IV Use

10 Vials

TEVA

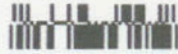
Each mL contains: 250 mg amikacin (as the sulfate), 0.66% sodium metabisulfite, 2.5% sodium citrate dihydrate, water for injection qs, air replaced with nitrogen. pH is adjusted with sulfuric acid and/or if necessary sodium hydroxide. pH: 3.5–5.5.

Usual Dosage: 15 mg/kg/day divided into 2 or 3 equal doses, IM.

Do not exceed 1.5 grams daily.
See Package Insert for IV and other uses.

Store at controlled room temperature 15°–30°C (59°–86°F).

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